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Preoperative Radiotherapy Improves Survival for Patients Undergoing Total Mesorectal Excision for Stage T3 Low Rectal Cancers

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Objective
To examine the effect of preoperative radiotherapy (PRT) on patients who undergo rectal resection with total mesorectal excision (TME) for stage T3 low rectal cancers.

Summary Background Data
Evidence for the value of PRT before rectal cancer surgery is weakened by variability in the use of TME. Many surgeons have concluded that PRT is unnecessary for small rectal tumors if TME is performed, but there are no prospective data to support this opinion.

Methods
Since 1980, 2,200 patients with rectal cancer have been enrolled in a prospective database. Of these, 259 underwent curative anterior or abdominoperineal resection with TME for pathologically confirmed T3 lesions within 8 cm of the anal verge. Patients were grouped by receiving PRT (n = 92) or not receiving PRT (n = 167). Five-year overall survival and 5-year local recurrence rates were evaluated.

Results
Overall survival was increased from 52% in patients not receiving PRT to 63% in those receiving PRT. PRT increased overall survival for node-negative patients from 58% to 82%, with no benefit for node-positive patients. There was no significant difference in local recurrence rates. When categorized by tumor size, there was no difference in overall survival or local recurrence for 0- to 2-cm tumors or those larger than 5 cm, but PRT increased overall survival from 50% to 72% for patients with 2- to 5-cm tumors. Similar results were observed for patients with tumors staged as T3 on preoperative endoluminal ultrasound.

Conclusions
Patients with pT3 low rectal cancers undergoing resection with TME have an improved survival with PRT. The effect is most beneficial for patients with node-negative and 2- to 5-cm tumors, although this group may include larger and node-positive tumors that have been downstaged by PRT. PRT should be advocated for all patients with T3 rectal cancers less than 8 cm from the anal verge, even if the surgery includes a properly performed TME.

Colorectal cancer is a leading cause of morbidity and mortality and ranks second to cancers of the lung and breast as a cause of death in men and women, respectively. Although endoscopic screening programs may reduce the incidence of cancer and the stage at which cancer is diagnosed, many patients present at an advanced stage of the disease. The 5-year survival rate of patients undergoing curative surgery is often only 50%, and local recurrence has been reported in as many as 35% to 40%.[1–4] Thus, radiotherapy has been investigated as an adjuvant therapy for rectal cancer in an effort to reduce rates of local recurrence and improve overall survival.

In 1988, a meta-analysis of six randomized controlled trials of preoperative radiotherapy (PRT) failed to show a significant beneficial effect on survival.[5] More recent randomized studies have suggested that PRT may be of benefit for rectal cancer.[2] This evolution in opinion has been supported by another more recent meta-analysis.[6] Thus, there is increasing clinical evidence to support the biologic rationale

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of giving radiotherapy before surgery,[7] at a time when the small bowel is freely mobile and not fixed in the pelvis by postoperative adhesions.

Although these studies suggest that PRT should be used more frequently for patients about to undergo rectal cancer surgery, several concerns have led many surgeons to be hesitant about freely recommending this form of therapy. The first is the difficulty of accurately knowing the tumor stage preoperatively, so as to select the best candidates for PRT. Clinical examination, endoluminal ultrasound, and computed tomography have been utilized to define the more advanced lesions that might derive most benefit from PRT. There is no consensus to the best test, but endoluminal ultrasound is becoming favored as the best and easiest test for low, nonobstructing tumors. Furthermore, once tumor stage has been defined, there are no definitive guidelines as to which stage lesions should receive PRT.

The second and more important issue is that there are no data concerning the effect of PRT for patients who have undergone a total mesorectal excision (TME). None of the randomized trials published to date have described formal TME, and in these trials, local recurrence rates in the surgery-only arms have been on the order of 25% to 50%,[1–4,6] much higher than the expected 4% to 9% seen with a formal TME.[8–12] Thus, many surgeons feel that PRT may subject patients to unnecessarily increased morbidity and mortality, especially when performed with a three-field technique. This is particularly so for small rectal tumors that can easily be removed by a TME technique. Nevertheless, until the completion of studies like the Dutch Colorectal Surgical study, which incorporates TME and preoperative radiation,[13] prospective data will not be available.

In an effort to address the above concerns, we examined the effect of PRT on the 5-year survival and 5-year local recurrence rates for patients undergoing surgery for stage T3 cancers within 8 cm of the anal verge. The primary analysis was performed for tumors staged as T3 by postoperative pathology. A second analysis was performed as a control, using a cohort of patients staged as T3 by preoperative endoluminal ultrasound performed before PRT.

METHODS

Patients were recruited from a prospectively maintained database in this department since 1980 for patients undergoing surgery for cancers of the colon and rectum. Approval from the Institutional Review Board was obtained.

Patients were selected who were undergoing anterior resection or abdominoperineal resection for adenocarcinoma of the rectum found to be less than 8 cm from the anal verge by clinical examination and rigid proctoscopy. In an effort to define the effect of PRT as accurately as possible, patients were excluded if they had proven distant metastatic disease at the time of surgery, although there was no policy of routine imaging of the liver by ultrasound or computed tomography before surgery. Patients were also excluded if they received postoperative radiotherapy or chemotherapy. Patients were not placed into "curative" and "palliative" groups, as performed in reports by other groups,[12,14] as this introduces an unnecessary subjective nature to examination of outcome in subgroups.

Pathologic reports were evaluated and patients with pathologically confirmed T3 tumors (pT3) were selected for analysis, regardless of nodal status. The largest diameter of the tumor and nodal status were documented. Data were examined as to the use of adjuvant radiotherapy or chemotherapy, excluding those who had any form of chemotherapy outside the time of PRT. Time from surgery until death or most recent follow-up was determined. Survival was defined as overall 5-year survival (OS) or cancer-specific 5-year survival (CS). Local recurrence (LR) was defined as recurrence within the pelvis, with or without distant recurrence.

As a control for the fact that tumor stage was being determined by postoperative pathology, and that some of these pathologically staged tumors may have been downstaged by the PRT, a second cohort of patients was selected from the database who had tumors staged as T3 on preoperative endoluminal ultrasound (uT3) performed before commencing PRT. In this department, PRT is generally advocated for those with larger, bulky tumors. Radiotherapy was given using 40 to 50 Gy over 4 to 6 weeks by either three or four portals. Surgery was performed within 4 to 6 weeks of completion of PRT.

Surgery was performed using the technique of total excision of the mesorectum with its investing layer of fascia, as described in previous reports from this institution.[8–10] Briefly, the avascular plane behind the inferior mesenteric vessels was defined before high ligation of these vessels. After ligating the inferior mesenteric vessels, the pelvic dissection was commenced. The fascial layer overlying the presacral autonomic nerves was carefully protected. This plane of dissection was followed to the pelvic floor, staying behind Denonvillier's fascia, except for anterior tumors, for which dissection was performed anterior to Denonvillier's fascia, and anterolateral tumors, for which only half of Denonvillier's fascia was removed. For patients undergoing anterior resection with coloanal anastomosis, dissection continued down to the anal canal, thereby removing the complete mesorectum. After clamping below the tumor, the rectum below the clamp was irrigated with 40% ethanol before division of the distal rectum. As explained in a previous report,[10] TME was not performed for high rectal tumors; however, for these tumors within 8 cm of the anal verge the complete mesorectal tail was excised as part of the mesorectal "package," in a manner similar to recent reports by other authors.[15]

All surgeons had received postgraduate training in the technique of TME and were practicing staff surgeons in a practice with a high volume of rectal surgery. Approximately 60% of the cases had been performed by the two senior surgeons in the department (V.W.F., I.C.L.).

Table 1. DEMOGRAPHIC, TUMOR, AND SURGERY-RELATED DATA

	No PRT	PRT	*P* Value
n	167	92	
Mean age at surgery (years)	65 ± 12	59 ± 13	.005 T
Age range at surgery (years)	24–97	18–88	
Male/female	112/55	71/21	.09 C
Mean follow-up (months)	42 (28–63)	41 (24–89)	.82 W
Range of follow-up (months)	1–170	1–179	
Anterior resection	73	47	.26 C
Abdominoperineal resection	94	45	
Mean level of tumor above anal verge for all cases (cm)	5.3 ± 1.5	5.2 ± 1.5	.65 T
Mean distal margin for cases with anastomosis (cm)	2.4 ± 1.3	2.5 ± 1.4	.30 T
Well differentiated	9	4	.12 M
Moderately differentiated	124	61	
Poorly differentiated	34	27	

PRT, preoperative radiotherapy; T, *t* test; W, Wilcoxon rank-sum test; C, chi-square; M, Mantel-Haenszel chi-square test.

Demographic, tumor, and surgery-related data were summarized within the PRT and no-PRT groups by means and standard deviations and ranges, with comparisons using the Student *t* test. Medians and interquartile range were used for nonparametric data, with the Wilcoxon rank sum. Categorical data were summarized by frequency within the groups, with the chi-square test for comparisons. Kaplan-Meier estimates, log-rank tests, and Cox regression analyses were used to correlate tumor size with 5-year OS, 5-year CS, and 5-year LR rates. Analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC).

RESULTS

Of 2,200 rectal cancer patients in the prospectively maintained database, 259 had undergone curative anterior or abdominoperineal resection with TME for pT3 adenocarcinomas less than 8 cm from the anal verge, without evidence of metastatic disease at the time of surgery, and had not received chemotherapy. Patients were grouped into those receiving PRT (n = 92) and those without PRT (n = 167). Median follow-up was 41 months (interquartile range 26–62), and demographic data are displayed in Table 1. Patients underwent similar surgical procedures for tumors of similar site, stage, and differentiation.

Initial evaluations were performed based on tumor nodal status (Table 2). PRT was associated with an improved survival, from 52% without PRT to 63% with PRT (P = .07); this was most notably seen for node-negative (N0) tumors (P = .002). There was also a trend to increasing mortality rates with increasing node positivity, but only for patients who did not receive PRT. The beneficial effect of PRT was lost for node-positive patients. It is possible that some of the N0 tumors may have been more advanced before PRT, and that they migrated stage to become node-negative after downstaging by PRT. Nevertheless, the ratio of N0, N1, and N2 patients in the PRT and no-PRT groups was identical after radiotherapy, suggesting that minimal stage migration may have occurred when categorized by nodal status. Of the patients who received PRT, 38 patients received concomitant preoperative chemotherapy and had an OS of 53.2%, while 54 did not and had an OS of 71.0% (P = .009, log-rank test).

Very similar results were seen for CS, with a significant improvement in survival for all patients, and particularly for node-negative patients. Although there was a 4% reduction in overall LR rates, this did not reach significance (see Table 2). Evaluation between patients who did and did not receive PRT based on nodal status using Cox regression analysis revealed a significant decrease in OS and CS, with a marginal increase in LR with increasing nodal status. The incidence of LR without distant metastasis was also established using Kaplan-Meier analysis. LR without distant metastatic disease occurred in 11.4% of patients who did not receive PRT and 8.7% of those who did (P = .6).

Results were next analyzed by the maximum diameter of the tumor on pathologic evaluation (Table 3). Patients with

Table 2. SURVIVAL AND RECURRENCE DATA BY NODAL INVOLVEMENT

	n		Overall 5-Year Survival (%)			Cancer-Specific 5-Year Survival (%)			Local Recurrence (%)		
	No PRT	PRT	No PRT	PRT	Log rank	No PRT	PRT	Log rank	No PRT	PRT	Log rank
All patients	167	92	52	63	0.07*	60	73	0.043*	17	11	0.46†
N0	87	48	58	82	0.002	68	90	0.004	11	9	0.82
N1	54	27	52	52	0.45	56	52	0.85	20	16	0.93
N2	26	15	31	32	0.59	62	64	0.51	32	0.0	0.08
N1, N2, N3	80	44	45	42	0.96	50	54	0.67	24	12	0.35

PRT, preoperative radiotherapy.
* $P < .001$ adjusting for age and number of nodes between groups, using Cox regression model.
† $P = .045$ adjusting for age and number of nodes between groups, using Cox regression model.

Table 3. SURVIVAL AND RECURRENCE DATA BY TREATMENT AND TUMOR SIZE

	n		Overall 5-Year Survival (%)			Cancer-Specific 5-Year Survival (%)			Local Recurrence (%)		
	No PRT*	PRT*	No PRT	PRT	Log rank	No PRT	PRT	Log rank	No PRT	PRT	Log rank
All patients	154	85	52	63	0.13†	60	73	0.026‡	17	11	0.45§
0–2 cm	12	17	49	38	0.86	49	52	0.39	14	16	0.59
2–5 cm	91	53	50	72	0.003	56	79	0.005	18	14	0.41
>5 cm	51	15	53	44	0.13	68	57	0.23	14	0	0.76

PRT, preoperative radiotherapy.
* Mantel-Haenszel chi-square evaluation of the proportion of patients in 0–2, 2–5, and over 5-cm groups for no PRT and PRT groups; level of significance $P = .001$.
† Comparison based on Cox regression model, adjusting for tumor size, number of nodes and age: tumor size $P = 0.39$; number of nodes $P < .001$.
‡ Comparison based on Cox regression model, adjusting for tumor size, number of nodes and age: tumor size $P = .14$; number of nodes $P < .001$.
§ Comparison based on Cox regression model, adjusting for tumor size, number of nodes and age: tumor size $P = .12$; number of nodes $P < .045$.

tumors 2 to 5 cm in size had a significant increase in OS from 50% to 72% ($P = .003$, log rank). A similar effect was seen for CS, which also reached significance for all tumors. The size of the tumor did not affect LR rates. Cox regression analysis between groups revealed that nodal status affected OS, CS, and LR, but tumor size did not. There was some stage migration based on tumor size, as the proportion of tumors over 5 cm in size was reduced from 31% to 16% in patients who had undergone PRT ($P = .001$, chi-square test).

Patients who underwent preoperative staging ultrasound were then evaluated as a control group to evaluate whether similar findings were present for tumors that were staged before radiation, and not by histopathology (Table 4). Once again, patients who had PRT had a significantly improved OS over those who did not, and the effect was most obvious for those with node-negative tumors. Improvements in CS did not reach statistical significance, presumably due to the smaller numbers who underwent endoluminal ultrasound. Once again, there was no obvious difference in LR rates between patients who did and did not receive PRT. Cox regression confirmed OS and CS to be poorer with increasing nodal status.

DISCUSSION

Cancers of the upper third of the rectum behave more like colonic cancer and have LR rates and a disease profile that differs from that of low rectal cancers.[10] Therefore, this study focused on cancers of the low rectum, for which PRT may have an important role in management. For tumors confined to the bowel wall, radiation is unlikely to be of benefit and may make surgery more difficult, while exposing the patient to radiation-related morbidity. This opinion has been supported by the recent meta-analysis of Camma et al,[6] in which patients with Dukes A tumors were found not to benefit from PRT. In contrast, if a tumor of the low rectum presents with advanced T4 disease, there is more of a consensus to give PRT, although the evidence would suggest that this is more helpful at reducing LR rates than improving survival.[4,16]

For patients with T3 tumors, it is more difficult to make a correct decision about PRT. Some surgeons believe that patients with small T3 lesions should simply undergo surgery with TME without radiotherapy, while only patients with larger fixed tumors should receive PRT.[14] Indeed, this was our opinion until the current study was performed,

Table 4. KAPLAN-MEIER ESTIMATES

	n		Overall 5-Year Survival (%)			Cancer-Specific 5-Year Survival (%)			Local Recurrence (%)		
	No PRT	PRT	No PRT	PRT	Log rank	No PRT	PRT	Log rank	No PRT	PRT	Log rank
All patients	29	39	58	87	0.044*	68	92	0.14†	16	18	0.31‡
N0	15	26	66	96	0.011	92	100	0.12	8	20	0.73
N+	14	13	31	70	0.32	29	76	0.18	24	0	0.07

PRT, preoperative radiotherapy.
* $P = .06$ adjusting for number of nodes between groups, using Cox regression model.
† $P = .006$ adjusting for number of nodes between groups, using Cox regression model.
‡ $P = .55$ adjusting for number of nodes between groups, using Cox regression model.

although it is impossible to make an evidence-based decision from the literature.

Based on our data, patients with T3 rectal cancers less than 8 cm from the anal verge should undergo PRT. This confers an improvement in survival and a reduction in LR to these patients. This effect is most beneficial for node-negative tumors and tumors 2 to 5 cm in size. As the downstaging effect from PRT is variable[17,18] and the effect on an individual patient is unpredictable, all patients with T3 or T4 tumors should receive PRT, regardless of tumor size or nodal stage. This recommendation may change in the future as we develop molecular methods or new imaging modalities[18] that can define which tumors are best suited to PRT.

Could PRT be reserved for those with tumors estimated to be 2 to 5 cm in greatest diameter, as they account for the majority of the improvement in outcome in this study? In our opinion, this would be inappropriate at the current time, as the lack of significant effect for tumors under 2 cm may well be due to the smaller numbers in this group. Moreover, tumors in the 0- to 2-cm group may well include larger tumors that have been downstaged by the PRT that have already derived some benefit from DXT. Similarly, the lack of benefit for tumors over 5 cm in the PRT group may relate to the fact that tumors remaining in this group are those that already have a poorer prognosis as they are insensitive to radiotherapy.

Although this is not a randomized controlled trial, there are several strengths to the data presented in this study. The procedure of TME has been performed by this experienced group of surgeons for many years and uses a well-established and standardized technique, with a high percentage of anterior resections, even though these tumors are all within 8 cm of the anal verge. Furthermore, this report gives an accurate indication of the results of TME combined with radiation in a large institution with a high-volume rectal surgical practice. This fulfils the increasingly recognized importance of having such surgery performed by surgeons who perform high volumes of surgery, in institutions that see high volumes of rectal cancer.[19,20]

It could be argued that by using pathologic staging for this study, the stage of tumors before PRT cannot be accurately defined. Although this is a valid point, this does not weaken the results presented. If anything, radiation would be shrinking some larger and more advanced tumors, making them be compared to smaller, less advanced tumors in the patients who did not receive PRT. As the PRT group still do better with this inherent disadvantage, we would suggest that the benefit of PRT is a real phenomenon. Furthermore, the analysis based on preoperative endoluminal staging of uT3 tumors reveals an almost identical beneficial effect for PRT, although the numbers are smaller in each group.

Patients with T3 low rectal cancers undergoing a rectal resection with TME have an improved survival with PRT. As there is currently no test that predicts which tumors will respond to radiotherapy, we recommend PRT for all patients with T3 rectal cancers less than 8 cm from the anal verge, even if the surgery includes a properly performed TME.

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